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<p>The research effort was to determine theoretically a physical basis for the interaction of low-intensity externally applied electromagnetic fields with biological tissue. The primary aim of the investigation was to establish a molecular basis for the class of interactions commonly referred to as nonthermal effects of electromagnetic fields with biological systems. In particular, the biological structure of interest was the plasma-membrane since it had been either directly or indirectly implicated in numerous experimental studies. (1) It was demonstrated how a membrane undergoing a phase transition could qualitatively account for the release and/or uptake of divalent calcium ions. (2) A characterization of changes in the structure of the membrane/electrolyte interface due to field induced changes in enzymatic activity was demonstrated. (3) The role of critical phenomena was shown analytically to be able to account for the unique sensitivity of biomembranes to weak external field perturbations, and describe alterations in the passive transport of sodium ions in rabbit erythrocytes.</p>			
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FINAL REPORT ON CONTRACT N00014-83-C-0008

TITLE: Calcium Displacement Caused by Electromagnetic Fields

Co-Principal Investigators: J. D. Bond and C. A. Jordan

INTRODUCTION

This research effort was to determine theoretically a physical basis for the interaction of low-intensity externally applied electromagnetic fields with biological tissue. Various anomalous responses of tissue at the cellular level have been observed which cannot be understood in terms of classical dielectric response theory. Examples of such responses are the anomalous release and/or uptake of divalent calcium ions from the neuronal cell surface during ELF field exposure and the anomalous enhancement of passive sodium ion permeability in red blood cells concomitant with microwave exposure.

The primary aim of the investigation was to establish a molecular basis for the class of interactions commonly referred to as nonthermal effects of electromagnetic fields with biological systems. In particular, the biological structure of interest was the plasmamembrane since it had been either directly or indirectly implicated in numerous experimental studies.

Techniques from the physics and chemistry of interfaces and from the physics of phase transitions were used extensively in this work.

GOALS

The specific goals of this project were to:

- Examine changes in the structure of the electrical double layer at the membrane/extracellular electrolyte interface subsequent to changes in activity of membrane bound enzymes due to external electromagnetic fields;
- Study the possible role of membrane phase transitions in mediating a cellular response to an electromagnetic field.
- Conduct workshops and colloquia to properly integrate both experimental and theoretical research in the bioelectromagnetics area, and to disseminate any critical reviews and analyses of the scientific literature to the international bioelectromagnetics community.

RESULTS

The above mentioned goals were all met. In addition, a number of publications in peer reviewed journals, a book, three book chapters, an average distribution of 10 international newsletters a year, a number of invited talks, as well as contributed papers, workshops, symposia, and colloquia (including synopses) resulted from this effort. The book, Electroporation and Electrofusion in Cell Biology, was forwarded to ONR's COTR under separate cover and is to be considered as part of this final report. (The publication release date by Plenum Press was late summer 1989.)

The publications, listed in this report, provide detailed accounts of the work accomplished. Highlights of the results are as follows:

- It was demonstrated how a membrane suffering a phase transition could qualitatively account for the release and/or uptake of divalent calcium ions;
- A characterization of changes in the structure of the membrane/electrolyte interface due to field induced changes in enzymatic activity was demonstrated;
- The role of critical phenomena, i.e. a membrane phase change occurring at or near a thermodynamic critical point was shown analytically to be able to:
 - account for the unique sensitivity of biomembranes to weak external field perturbations;
 - describe explicitly alterations in the passive transport of sodium ions in rabbit erythrocytes.
- Numerous suggestions were provided to the experimental community for additional experiments to be performed in order to not only test our theoretical prediction, but to provide additional insight into interaction mechanisms (molecular) between external fields and biological membranes.

GENERAL REMARKS

Without a doubt, what the field commonly referred to as bioelectromagnetics sorely needs is a much greater interaction between theorists and experimentalists. To physicists, such collaboration is tacitly understood. The prevailing modus operandi, however, among many biological scientists is to do an experiment and "model" the results themselves. In some instances, such an approach has met with success; however, when dealing with extraordinarily complex systems (biological systems) and attempting to describe their behavior at the molecular level, competent theoretical guidance is essential. Success in understanding the basic mechanism of interaction of fields with membranes is most likely to be gained by the establishment of well-designed and well-organized interdisciplinary efforts.

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PUBLICATIONS

Rozzell, T. C. and C. A. Jordan, eds., "Electromagnetic Fields and Cell Biology: Scientific Issues and Research Opportunities," Science Applications International Corporation. (1989)

Bond, J.D. and N.C. Wyeth, "Are Membrane Microwave Effects Related to a Critical Phase Transition?," J. Chem. Phys., 85, 7377-7379. (1986)

Bond, J.D., and N.C. Wyeth, "Alterations in the Structure of the Electrical Double Layer Adjacent to a Charged Membrane Due to Electromagnetic Induced Changes in the Activity of Membrane Bound Enzymes," Cell Biophysics, 7, 293-304. (1985)

Bond, J.D. and C.A. Jordan, "Electrostatic Influences on Electromagnetically Induced Calcium Ion Displacement from the Cell Surface," Bioelectrochemistry and Bioenergetics, 12, 177-182. (1984)

Bond, J.D., and C.A. Jordan, "Nonionizing Electromagnetic Field Interactions with Biological Membranes: A Review of Athermal Mechanisms," Science Applications Reprint. Copyright (1983)

BOOK CHAPTERS AND BOOKS EDITED

Neumann, E., A. Sowers, and C.A. Jordan (Eds.), Electroporation and Electrofusion in Cell Biology, Plenum Press. (1989)

Bond, J.D. and N.C. Wyeth, "Membranes, Electromagnetic Fields and Critical Phenomena," in Mechanistic Approaches to Interactions of Electric and Electromagnetic Fields with Living Systems, Martin Blank, editor, Plenum Press. (1987)

Bond, J.D. and G.C. Huth, a chapter entitled "'Electrostatic Modulation of Electromagnetically Induced Nonthermal Responses in Biological Membranes," in Modern Bioelectrochemistry, edited by F. Gutmann and H. Keyzer, Plenum Press, NY. (1986)

Bond, J.D. and N.C. Wyeth, "Alterations in the Structure of the Electrical Double Layer Due to EM Coupling to Membrane Bound Enzymes," in Electrical Double Layers in Biology, Martin Blank, ed., Plenum Press. (1986)

Huth, G.C., J.D. Bond, and P.A. Tove, "Nonlinear Tunneling Barriers at High Frequencies and Their Possible Logic Processing Function in Biological Membranes," a chapter in Nonlinear Electrodynamics in Biological Systems, A.F. Lawrence and W.R. Adey, editors, Plenum Press, NY. (1984)

SPECIAL INVITATIONS

Participate at the Joint Meeting of the American Society for Biochemistry and Molecular Biology and the American Society for Cell Biology Symposium on "Electromagnetic Fields and Cell Biology: Scientific Issues and Research Opportunities," San Francisco. (30 January 1989) (C. Jordan)

Participate at the 1986 American Association for the Advancement of Science Annual Meeting Symposium on "Electrofusion and Electroporation in Cells and Protoplasts," Philadelphia, PA. (25-30 May 1986) (C. Jordan)

Participate at the 1985 Royal Society of Chemistry Faraday Symposium on "Phase Transitions in Adsorbed Layers," Oxford University, Oxford, England. (17-18 December 1985) (J. Bond)

Participate at the 1984 Gordon Conference on Bioelectrochemistry and Bioenergetics. (Summer 1984) (J. Bond)

Participate at the 1984 NATO Advanced Research Workshop on "Electromagnetic Interactions with Cells," Erice, Sicily. (17-28 September 1984) (J. Bond)

Guest Scientist, Teknikum, Uppsala University, Uppsala, Sweden. (May 1983) (J. Bond)

Participate at the 1983 special symposium on "Techniques in Studies of Biological Effects of Low Level Millimeter Waves," Herrsching, West Germany. (4-6 September 1983) (J. Bond)

CONTRIBUTED TALKS

Bond, J.D. and N.C. Wyeth, "Electromagnetic Perturbations on Critical Phase Transitions in Lipid Bilayers," Bioelectromagnetics Society Abstr. (1986)

Bond, J.D., "Membranes, Microwaves, and Broken Symmetry," Joint Seminar of the Division of Biomedical Engineering, National Institutes of Health, and the Engineering in Biology and Medicine Society of the IEEE, NIH Campus. (February 1986)

Bond, J.D. and N.C. Wyeth, "The Influence of Electromagnetic Perturbations on Critical Phase Transitions in Lipid Bilayers," Royal Society Faraday Symposium, Oxford University, Oxford, England. (December 1985)

Bond, J.D., "Microwave Induced Passive Na⁺ Permeability at the Erythrocyte Membrane Phase Transition," Bioelectromagnetics Society Abstr. (1985)

Bond, J.D. and N.C. Wyeth, "Electromagnetic Effects on Double-Layer Structure," NATO Advanced Research Workshop, Erice, Sicily. (September 1984)

Bond, J.D., D.C. Mikulecky, and C.A. Jordan, "A Model for Alterations in RF Induced Ca²⁺ Efflux Based on Changes in the Structure of the Electrical Double Layer at an Enzymatic Surface," Bioelectromagnetics Society Abstr. (1984)

Bond, J.D. and C.A. Jordan, "Electrostatic Influences on Electromagnetically Induced Calcium Displacement from the Cell Surface," International Symposium of the Bioelectrochemistry Society, Stuttgart, Germany. (July 1983)

Bond, J.D., C.A. Jordan, and S.P. Almeida, "An Analysis of Cooperative Effects in Exploring the Coupling of Weak Electric Fields to Biological Membranes," Bioelectromagnetics Society Abstr. (1983)

Bond, J.D., C.A. Jordan, S.P. Almeida, and J.F. Soukup, "An Analysis of Ca^{+2} Binding to Cerebral Tissue Concomitant with Exposure to Low Intensity RF Electromagnetic Fields." Bioelectromagnetics Society Abstracts, P. 31. (1982)

INVITED TALKS

Bond, J.D. and N.C. Wyeth, Symposium on Bioelectric Phenomena, Northeast IEEE Conference, University of Pennsylvania. (March 1987)

Bond, J.D., and N.C. Wyeth, Symposium on Electrochemical and Ionic Mechanisms in Electromagnetic Cell Stimulation, Boston, MA. (May 1986)

Bond, J.D., Symposium on Electromagnetic Effects in Biomembranes, University of Texas. (December 1985)

Bond, J.D. and N.C. Wyeth, Symposium on Electrical Double Layers in Biology, Toronto, Canada. (May 1985)

Bond, J.D., American Chemical Society Symposium on "Bioelectrochemistry: Ions, Membranes, and Surfaces." (August 1983)

Huth, G.L., J.D. Bond, and P.A. Tove, International Conference on Nonlinear Electrodynamics in Biological Systems, Loma Linda, CA. (7 June 1983)

Bond, J.D., Third International Workshop on Nonlinear Electromagnetic Interaction with Biological Tissue, University of Maryland. (November 1983)

WORKSHOPS AND COLLOQUIA

Workshop on "Phase Transitions and Critical Phenomena in Biomembranes" which included prototypes and the role such transitions play in mediating electromagnetic interactions with these systems. National Institutes of Health, Bethesda, MD. (1-2 October 1986). Approximately 40-50 scientists in attendance.

Workshop on the "Biological Effects of High-Frequency Electromagnetic Fields" which included molecular experiments (i.e., effects on DNA), and theories to include vibrational, electronic and cooperative response. Asilomar, Pacific Grove, CA. (28-30 April 1985). Approximately 40-50 scientists in attendance.

Workshop on the "Biological Effects of Low Frequency Magnetic Fields" which included pulsed magnetic fields, the influences of constant low-level magnetic fields on ac effects, and stimulation of growth and regeneration of soft tissue. Airlie House, Airlie, VA. (11-13 November 1984). Approximately 20 scientists in attendance.

Dr. Richard B. Frankel, Massachusetts Institute of Technology, Colloquium on "Magnetite and Magnetic Navigation in Bacteria," Uniformed Services University of Health Sciences. (2 May 1984)

Dr. Friedrich Kremer, Max-Planck-Institut fur Festkorperforschung, Stuttgart, Colloquium on "The Non-Thermal Influences of MM-Waves on Biological Systems," Uniformed Services University of Health Sciences. (14 January 1984)

Dr. Alan Bishop, Los Alamos National Lab, Colloquium on "Solitons in Synthetic and Biological Polymers," Uniformed Services University of Health Sciences, (10 November 1983)

Prof. Herbert A. Pohl, Oklahoma State University, Colloquium "Biological Dielectrophoresis: Applications to Cell Fusion, Rotation, and Characterization of Natural Radio Emissions," National Center for Devices and Radiological Health, Food and Drug Administration. (26 May 1983)

Prof. E. H. Grant, University of London, Colloquium on "Electrical Properties of Tissue and Their Role in Stimulated Tissue Regeneration and Other Biological Phenomena," National Institutes of Health. (20 April 1983)

Dr. Barnett Rosenberg, Michigan State University, Colloquium on "Monitoring Brain and Heart Function by Microwave Scattering," National Institutes of Health. (3 March 1983)

Dr. C. Andrew L. Bassett, Columbia University, Colloquium on "Biomedical Implications of Pulsed Electromagnetic Fields (PEMFs)," National Institutes of Health. (26 January 1983)

Dr. Arthur Pilla, Mt. Sinai School of Medicine, Colloquium on "Cellular Mechanisms Involved in Biomedical Applications of Pulsed Electromagnetic Fields," National Institutes of Health. (8 December 1982).

DISTRIBUTION LIST

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INVESTIGATORS

Dr. W. R. Adey
J. L. Pettis Memorial VA Hospital
11201 Benton Street
Loma Linda, CA 92357

Dr. Stephen Cleary
Virginia Commonwealth University
Box 694 - MCV Station
Richmond, VA 23298

Dr. C. C. Davis
Department of Electrical Engineering
University of Maryland
College Park, MD 20742

Dr. Carl Durney
Department of Electrical Engineering
University of Utah
Salt Lake City, UT 84112

Dr. Kenneth R. Foster
Bioengineering Department
University of Pennsylvania
Philadelphia, PA 19104

Dr. Reba Goodman
Columbia University
630 West 168th Street
New York, NY 10032

Dr. A. W. Guy
Department of Rehab. Medicine, RJ-30
University of Washington
Seattle, WA 98195

Ms. Carol Jordan
SAIC, 1710 Goodridge Drive
P.O. Box 1303
McLean, VA 22102

Dr. Adrianus J. Kalmijn
Scripps Institution of Oceanography
Ocean Research Division, A-020
La Jolla, CA 92093

Dr. Bruce Kleinstein
Information Ventures, Inc.
1500 Locust Street
Philadelphia, PA 19102

Dr. Raphael Lee
Department of Electrical Engineering
and Computer Science
Massachusetts Institute of Technology
Cambridge, MA 02139

Dr. S. M. Lindsay
Department of Physics
Arizona State University
Tempe, AZ 85287

Dr. Thomas C. Rozzell
National Research Council, FG 424
2101 Constitution Avenue
Washington, DC 20418

Dr. Asher Sheppard
Research Service 151
J. L. Pettis Memorial VA Hospital
Loma Linda, CA 92357

Dr. Betty Siskin
Wenner-Gren Research Laboratory
University of Kentucky
Lexington, KY 40506

Dr. Arthur E. Sowers
American Red Cross
Holland Laboratory
15601 Crabbs Branch Way
Rockville, MD 20855

Dr. Shiro Takashima
Bioengineering Department
University of Pennsylvania
Philadelphia, PA 19104

Dr. Watt W. Webb
Department of Applied Physics
Cornell University
Ithaca, NY 14853

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ADMINISTRATORS

Scientific Officer, Biophysics Program
Code 1141SB
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

Program Manager
Biological/Human Factors Division
Office of Naval Research, Code 125
800 N. Quincy Street
Arlington, VA 22217-5000

Program Manager, Molecular Biology
Code 1141MB
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

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